Pidotimod for Covid-19

Pidotimod para Covid-19

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Abstract

Covid-19 was the third leading cause of death in all of 2020, but in December 2020 and the beginning of 2021, the disease suddenly spiked and briefly became the number one cause of death in the United States (U.S.), particularly among those aged 35 years or older even though as of June 30, 2021, about 66% of adults in the U.S. have received at least one Covid-19 vaccine dose. At present, there is no drug to treat Covid-19 that can reduce the morbidity and mortality significantly, which has brought great panic to the society and scientific community. Antiviral agents and immune-modulating treatments are currently being trialed. Searches were conducted in PubMed, ScienceDirect, Google Academic, LitCovid, and MedRxiv for studies published from the beginning of 2000 through April 2021 that tested the clinical uses of pidotimod. Articles were selected prioritizing randomized clinical trials, systematic reviews, and clinical practice guidelines. Research results showed that Immunotherapy proved to be an effective method for fighting against similar viral infections to Covid-19 such as SARS-COV, and Middle East respiratory syndrome coronavirus (MERS-COV). studies aimed to dilucidated the mechanism of action of pidotimod, as well as randomized clinical trials that evaluate the security and utility of the drug are needed. In this scenario, the administration of Pidotimod could represent a potentially innovative strategy. In conclusion, in patients with Covid-19 without pneumonia, pidotimod could be considered an option, well-tolerated, and associated with a rapid reduction of systemic symptoms of the disease.

KEY WORDS

Immunostimulation, Immunotherapy, Pidotimod, Covid-19, treatment.

Resumen

La Covid-19 fue la tercera causa de muerte en todo el año 2020, pero en diciembre de 2020 y principios de 2021, la enfermedad se disparó repentinamente y se convirtió brevemente en la primera causa de muerte en los Estados Unidos (EE.UU.), en particular entre las personas de 35 años o más, a pesar de que, a partir del 30 de junio de 2021, alrededor del 66% de los adultos en los EE.UU. habían recibido al menos una dosis de la vacuna Covid-19. En la actualidad, no existe ningún fármaco para tratar la Covid-19 que consiga disminuir la morbilidad y mortalidad de manera significativa, lo que ha provocado un gran pánico en la sociedad y la comunidad científica. Actualmente se están ensayando agentes antivirales y tratamientos inmunomoduladores. Se realizaron búsquedas en PubMed, ScienceDirect, Google Academic, LitCovid y MedRxiv de estudios publicados desde principios de 2000 hasta abril de 2021 que evaluaron los usos clínicos del pidotimod. Se seleccionaron los artículos priorizando los ensayos clínicos aleatorizados, las revisiones sistemáticas y las guías de práctica clínica. Los resultados de la búsqueda mostraron que La inmunoterapia demostró ser un método eficaz para luchar contra infecciones virales similares a la Covid-19, como el SARS-COV y el coronavirus del síndrome respiratorio de Oriente Medio (MERS-COV). Se necesitan estudios orientados a dilucidar el mecanismo de acción del pidotimod, así como estudios clínicos aleatorizados que evalúen la seguridad y utilidad del fármaco para tratar la Covid-19. En este escenario, la administración de Pidotimod podría representar una estrategia potencialmente innovadora. En conclusión, en pacientes con Covid-19 sin neumonía, el pidotimod podría considerarse una opción, bien tolerada y asociada a una rápida reducción de los síntomas sistémicos de la enfermedad.

PALABRAS CLAVE

Inmunoestimulación, Inmunoterapia, Pidotimod, Covid-19, tratamiento.

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Introduction

A case of unidentified viral pneumonia was first reported in Wuhan, Hubei Province, China, in December 2019. Over the following weeks, the virus of unknown origin gradually spread around the world, and on January 7, 2020, a chinese scientific institute research announced that viral pneumonia was a new type of coronavirus called Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), later named by the World Health Organization (WHO) as Coronavirus Disease 2019 (Covid-19).[1,2] On 24 February 2020, the WHO acknowledged that the SARS-COV-2 has the potential to spread globally and cause a pandemic outbreak.[3,4] Finally, on 11 March 2020, the WHO declared the Covid-19 outbreak as a pandemic.[5] Acute respiratory infections (ARIS) are one of the most frequent infections in both adults and children.[6]

Most Covid-19 cases either are asymptomatic (35.1 %)or result in only mild disease (up to 81 % in some series).[1,2] However, in some patients, a respiratory illness requiring hospital care develops, and such infections can progress to critical illness with hypoxemic respiratory failure requiring prolonged ventilatory support.[7] Covid-19 was the third leading cause of death in all of 2020, but in December 2020 and the beginning of 2021, the disease suddenly spiked and briefly became the number one cause of death in the United States (U.S.), particularly among those aged 35 years or older; even though as of June 30, 2021, about 66 % of adults in the U.S. have received at least one Covid-19 vaccine dose.[8,9] By November 17, 2021, according to Worldometer,[10] there had been 255,461,803 confirmed cases, 5,135,235 reported deaths, and 230,901,818 recovered persons worldwide.

At present, there is no specific drug in clinical practice, which has brought great panic to the society and scientific community. Antiviral agents and immune-modulating treatments are currently being trialed.[11] Immunotherapy is an effective method for fighting against similar viral infections such as SARS-COV, and Middle East respiratory syndrome coronavirus (MERS-COV); these methods include several types of vaccines, monoclonal antibody candidates, and others.[12] Modulation of immunity with pidotimod has emerged as a novel therapeutic approach.[13-16]

Pidotimod is a synthetic dipeptide that exerts immunostimulatory effects by affecting both innate and adaptive immunity and has been investigated for more than two decades. Numerous studies have assessed the efficacy and safety of pidotimod in both adults and children in different conditions such as recurrent respiratory infection (RRI), asthma, bronchitis, chronic obstructive pulmonary disease (COPD), and pneumonia.[6,16] It is clinically evident that immunostimulants play a crucial role in the case of respiratory disease. Among the currently available immunostimulants, pidotimod is the most effective for respiratory disease and there is evidence that showed positive effects of this immunotherapy in adult patients with and without Covid-19 pneumonia.[17-19]

Objetive

In this article, we review the clinical potential evidence for pidotimod as an alternative new treatment for Covid-19.

Methodology of bibliographic research

Searches were conducted in PubMed, ScienceDirect, Google Academic, LitCovid, and MedRxiv for studies published from the beginning of 2000 through April 2021. Articles relevant to general medical readers were selected, prioritizing randomized clinical trials, systematic reviews, and clinical practice guidelines using the keywords pidotimod, immunostimulation, Covid-19 and treatment.

Coronavirus Disease 2019 (Covid-19)

Coronavirus (CoV) is derived from the Latin word "corona" meaning "crown".[20] CoV are RNA viruses of the subfamily Coronavirinae that belong to the family Coronaviridae and the order Nidovirales. CoV causes respiratory infections in warm-blooded creatures, such as bats, camels, and veiled palm civets in avian species. The most common symptoms of coronavirus disease can change over diverse host species. In humans, coronavirus infection may be asymptomatic or accompanied by fever, cough, dyspnea, gastrointestinal inflammation and, in some cases, it causes a range of respiratory tract infections varying from mild cold to severe respiratory distress syndrome.[21,22]

From the point of view of taxonomic categorization, SARS-COV-2 (Covid-19) is one of the many viruses of the species, CoV related to SARS. However, SARS-COV and SARS-COV-2 vary in terms of the disease spectrum, modes of transmission, and also diagnostic methods.[22,23]

Covid-19 is an infectious disease that causes severe acute respiratory syndrome, a characteristic hyperinflammatory response, vascular damage, microangiopathy, angiogenesis, and widespread thrombosis.[24] Human-to-human spread of Covid-19 from patients to healthcare workers and flight attendants who were in close contact with infected patients have also been reported. Spread occurs by common pathways such as direct transmission, contact transmission, and airborne transmission through droplets and during medical procedures. Common modes of spread are coughing, sneezing, droplet inhalation, and contact with oral, nasal, and ocular mucous membranes. Viral dissemination occurs in the respiratory tract, saliva, feces, and urine.[21,22,25]

Four Covid-19 stages were identified: the first stage is characterized by upper respiratory tract infection; the second by the appearance of dyspnea and pneumonia; the third by a clinical deterioration with a cytokine storm and subsequent hyperinflammatory state; and the fourth by death or recovery.[24] The most common symptoms of Covid-19 are nonspecific, mainly consisting of fever, malaise, cough, and muscle pain. Other minor symptoms are sore throat, headache, chills, nausea or vomiting, diarrhea, senility, and conjunctival congestion. Covid-19 is mild to moderate illness (not pneumonia and pneumonia), severe illness (dyspnea, respiratory rate> 30 / min, oxygen saturation <93 %, PaO2 / FiO2 ratio <300 and / or pulmonary infiltrates) are classified clinically. More than 50 % of lung fields within 2 - 8 hours) and severe (respiratory failure, septic shock, and/or multiple organ dysfunction/ failure).[22]

There are several pathophysiological features of severe Covid-19, a pneumonic process characterized by intense radiologic opacity is associated with extensive alveolar destruction, inflammatory infiltrates, microvascular thrombosis, and inflammatory organ injury in a subgroup of patients having markedly elevated levels of inflammatory markers, including C-reactive protein, ferritin, interleukin-1, and interleukin-6.[7]

Human-to-human transmission of Covid-19 depends mainly on the receptor-binding domain of the spike protein and its host receptor ACE2.[23] High expression of ACE2 has been identified in humans in the lung (type II alveolar cells), esophagus, ileum, colon, kidney (proximal convoluted tubules), myocardium, bladder (urothelial cells) and, in the oral mucosa. ACE2 receptors facilitate viral entry into host cells and subsequent viral replication. The principal factors implicated in Covid-19 viral pathogenesis are the spike 1 subunit protein, priming by the transmembrane protease serine-2 (essential for viral entry and replication), ACE2-Covid-19 receptor interaction, and ACE2 protein down-regulation.[21,22]

The diagnosis of Covid-19 is usually made employing nasal swabs, which are studied by polymerase chain reaction (PCR) testing. However, in several circumstances it is not usually reliable due to the different sensitivity it may present in patients; therefore, complementary studies will be required to

establish an accurate diagnosis using clinical analysis, laboratory, and imaging findings.[26]

PCR study for the detection of SARS-COV-2 RNA obtained from the respiratory system via nasal swab test is considered the gold standard for timely diagnosis; also, there are traces of SARS-COV-2 nucleic acid in the gastrointestinal tract, urine, and saliva.[26,27] However, it will depend on the stage of infection at which the test is performed.[26] According to several studies to evaluate the sensitivity of this test, it was found that on the fourth day after exposure there was a sensitivity of 33 %, 62 % on the day symptoms began, and 80 % three days after the onset of symptoms.[28,29]

In laboratory tests, the most frequently found findings are lymphopenia, leukopenia, and hypoalbuminemia; this is due to the overproduction of cytokines and inflammatory markers. Regularly, these data indicate the onset of Cytokine Release Syndrome (CRS) in patients, which translates into an increased risk of complications such as Severe Acute Respiratory Distress Syndrome (ARDS) or even death.[27]

Pidotimod

Chemically, pidotimod is 3-L-pyroglutamic-L-thiazolidine-4-carboxylic acid. It is a synthetic dipeptide molecule with immunostimulatory activity and was introduced in Italy in 1993 and subsequently in some other European countries (Russia, Ukraine, and Greece), China, Mexico, and other Central and South American countries. The drug is not authorized in most European countries or North America.[13,30]

Pidotimod is a synthetic oral immunostimulant, which has a regulatory and stimulatory role in the cell-mediated immune response.[18] Pidotimod's immunostimulatory activity focuses on two immune responses: adaptive immunity and innate immunity. Pidotimod induces dendritic cells (DCS) maturation, significantly improve IgA and IgG levels in the body, regulate the generation of antibody, promotes phagocytosis, upregulates expression of toll-like receptors-2 (TLR-2) and HLA-DR (human leukocyte antigen – antigen D related), stimulates T cell differentiation toward Th-1 type, proliferation towards Th1 phenotype, inhibits thymocyte apoptosis, promotes phagocytosis, increase salivary immunoglobulin (Ig) IgA levels, and enhances the function of natural killer (NK) cells.[13,16,31]

Pharmacokinetic studies evidenced that the drug was absorbed quickly by oral administration. The bioavailability upon oral administration in humans was 45 % and the half-life was 4 hours.[13,32] Both animal and clinical trials have provided evidence that, although Pidotimod does not have direct antibacterial and antiviral activity, it may play an essential role in the treatment of bacterial and viral infections by enhancing the body's immune function.[33]

Pidotimod, as said previously, significantly increased TLR-2 (toll-like receptor-2) expression in BEAS-2B cells, a human bronchial epithelial cell line infected with a replication-defective adenovirus virus. In addition, inhibits the phosphorylation of ERK 1/2 (extracellular signal-regulated kinases 1 and 2) and, together with TNF-α, induced NF-kB (nuclear factor kappa-light-chain-enhancer of activated B cells) protein expression in the cytoplasm and its translocation to the nucleus. NFk-B plays a complex role in inflammation, and there is evidence for both pro-inflammatory and anti-inflammatory roles in the NF-kB pathway.[34]

Pidotimod was very well tolerated in the studies reviewed by Zhao et. Al,[34] with only isolated cases of nausea, vomiting, diarrhea, heartburn, abdominal pain, rash and headache, mostly mild to moderate vomiting, diarrhea, heartburn, abdominal pain, rash and headache, mostly mild to moderate. In randomized controlled trials (RCTS), there were isolated cases of mostly mild to moderate nausea, vomiting, diarrhea, heartburn, abdominal pain, rash, and headache that resolved after discontinuation of the drug. In the RCTS, there were there was no difference in the incidence of adverse effects between pidotimod and placebo.

Clinical Applications of Pidotimod

Different studies talk about the clinical uses in different respiratory diseases, as well as immunologically mediated ones. The common endpoint of these studies is that Pidotimod has an immunomodulatory activity which is able both to improve the clinical conditions of patients and to enhance and stimulate their immunity cells (lymphocytes but not only) functions acting on adaptive and innate immunity.[31]

The main clinical outcomes are the reduction of the number of infectious episodes, lesser severity of signs and symptoms, and, consequently, a reduction in the use of antibiotics and symptomatic drugs, visits to a pediatric clinic, absenteeism from school and Work, less mortality and morbidity in children with respiratory infections different from Covid-19.[13,31]

According to studies conducted on patients with atopic asthma, it seems that Pidotimod could affect T-lymphocytes balance with a possible additional anti-allergic activity.[35] Furthermore, it has been demonstrated an improvement of FEV1 and PEF in asthmatic patients treated with Pidotimod.[34] Vargas Correa et al. studied 73 children with allergic rhinitis and asthma with RRIs who were treated with pidotimod and reported a significant reduction in the mean number of acute infectious episodes than that was before treatment ($P < 0.005$).[13]

Not only does it reduce reinfection rates, the need for antibiotics, and the number and severity of symptoms associated with recurrent respiratory tract infections, pidotimod also decreased disease burden and improved days off school/kindergarten/work; use of rescue medications; and consultation time and hospitalization.[13]

Children with acute bronchitis were randomized to control (pidotimod, 400 mg two times a day for 2 weeks and then 400 mg once a day for 2 months) and observation (pidotimod plus montelukast, n = 63) groups by Wang et al. Addition of montelukast to pidotimod resulted in a significant reduction of acute-phase proteins such as C-reactive protein (CRP), haptoglobin, a1-acid glycoprotein, cerocyanin (CER) and significant improvement in the number of CD3+, CD4+, and CD4+/CD8+ cells.[36] While most of the clinical evidence comes from studies in pediatric patients, there have been publications on randomized controlled trials in adults with chronic bronchitis.[13] These trials demonstrated a reduction in exacerbations of chronic bronchitis in 580 adults over 45 years of age using Pidotimod at a dose of 800mg/day for 60 days compared to the placebo group.[34]

The use of Pidotimod has been evaluated in older adults with immunosenescence, impaired innate and adaptive immune response, increased susceptibility of older adults to infectious diseases as well as inflammatory diseases. The incidence of lower respiratory tract infections increases with advancing age and pneumonia is one of the main causes of death in this age group.[34]

A study in children with M. pneumoniae pneumonia was made by Ma et al.[37] For 3-5 days, patients received either azithromycin alone or azithromycin and pidotimod together. Patients receiving only azithromycin had low CD4+ cell levels and a low CD4+/CD8+ cell ratio compared to healthy controls. Pidotimod treatment resulted in a significant increase in the number of these cells. This indicates that this drug regulates T-lymphocyte subsets, which may contribute to early recovery from pneumonia.

Trabattoni et al.[38] randomized 16 patients with Community-acquired pneumonia (CAP) treated with pidotimod (800 mg twice daily), standard antibiotic (levofloxacin 500 mg BID), and standard antibiotic alone. On the fifth day of therapy, immunological assessments showed that pidotimod, in addition to standard treatment, increased antimicrobial and immunomodulatory proteins.

In studies focused on the treatment of adults aged 40 to 85 years with lower respiratory tract infections, chronic obstructive pulmonary disease, and pneumonia, evidence was found indicating that pidotimod increases the efficacy of antibacterial treatments, reduces symptom scores, improves pulmonary function and overall therapeutic effects, reduces recovery time.[34]

D'Amato et al.[39] recruited adult patients with non-cystic fibrosis bronchitis in two or more lobes and more than four previous bronchial infections without obstructive flow limitation. Pidotimod (800 mg) once a day for 20 days per month was compared with no pidotimod for 6 months. Exhaled nitric oxide (FeNO) was enhaced significantly with pidotimod and deteriorated without it.

Discusion

Prevention and treatment of respiratory infections and, especially, of Covid-19 is an ambitious goal. Mechanism-oriented studies together with clinical intervention trials are necessary to test biologically plausible prevention ideas. In this scenario, the administration of Pidotimod could represent a potentially innovative strategy.[40]

Ucciferri et. Al,[19] assessed both efficacy and safety of pidotimod in patients with mild manifestations of SARS-COV-2 without any suggestive evidence of concurrent pneumonia. They enrolled SARS-COV-2-positive (Brescia-Covid Respiratory Severity Scale 0) patients with fever and cough without acute respiratory failure or sign of pneumonia without required treatment standard regimens or hospitalization from March to April 2020 at a Hospital in Chieti, Italy. Twenty patients assigned to SARS-COV-2 1:1 was enrolled and divided into group A (Pidotimod group: Pidotimod 800 mg twice daily orally for 10 days) and group B (control group: symptomatic regimens). The Pidotimod group evidenced earlier clinical resolution than the control group (4.10±2.18 vs. 7.50±2.63 days; 95% CI: 1.13 - 5.67, S.E.: 1.08; p=0.006). In conclusion, they strongly suggest that in adult ambulatory patients with SARS-COV-2 infection without pneumonia, pidotimod could be considered an option.

Zhang et. Al,[18] reported on February 2020, two suspected patients who had a history of contact with SARS-COV-2 and who used, occasionally with the treatment, pidotimod dispersible tablets. Their physical signs were very consistent with the clinical symptoms of Covid-19, but the infection was not confirmed by laboratory studies. After taking Pidotimod, signs were relieved rapidly.

Chatterje and Al Basir[17] investigated the potential role of pidotimod during the interactions between the SARS-COV-2 spike protein and the epithelial cell receptor ACE2 in the acute phase of Covid-19 infection. With the help of impulsive differential equations, they showed that appropriate dosage and dosing intervals are important for the eradication of infected cells and viruses, which might result in the control of the pandemic. It has also been found that the duration of the dosing interval and the drug dose play a very decisive role in controlling and eradicating the infection. A relevant prediction of their model is that effective therapy can often be obtained, even in the case of low adherence, if the dosing regimen is adjusted appropriately. Furthermore, if the treatment regimen is not properly adjusted, the therapy is not effective at all.

Conclusion

In conclusion, in adult patients with SARS-COV-2 infection without pneumonia, pidotimod could be considered an option, well-tolerated, and associated with a rapid reduction of systemic symptoms of the disease. Several interventions have some degree of evidence to improve the innate immune response and thus provide potential benefit, but specific trials in Covid-19 should be conducted to support strong conclusions.

Conflict of interest: None.

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